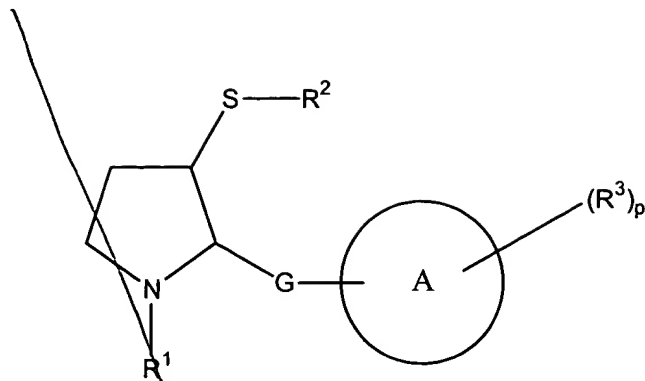


21

Sub

DI



Formula I

wherein:

R^1 is selected from H; $-C_{1-4}$ alkyl; $-CO-C_{1-4}$ alkyl; $-CO-O-C_{1-4}$ alkyl; $-CO-O-C_{2-4}$ alkenyl; $-C_{1-4}$ alkylene- $CONR^4R^5$ (wherein R^4 and R^5 are independently selected from H and C_{1-4} alkyl); $-C_{1-4}$ alkylene- $COOR^6$ (wherein R^6 is selected from H and C_{1-4} alkyl); $-C_{1-3}$ alkylene-Ph and $-CO-O(CH_2)_nPh$ wherein the phenyl groups in $-C_{1-3}$ alkylene-Ph and $-CO-O(CH_2)_nPh$ are optionally substituted by R^a and/or R^b and R^a and R^b are independently selected from C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, thiol, C_{1-4} alkylsulfanyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl and sulfonamido; and $n=0-4$;

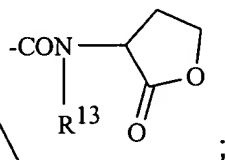
R^2 is selected from H; $-C_{1-4}$ alkyl; $-COC_{1-4}$ alkyl; and $-COOC_{1-4}$ alkyl; and $-C_{1-3}$ alkylene-Ph optionally substituted on the phenyl ring by R^a and/or R^b ;

R^3 is selected from H; OH; CN; CF_3 ; NO_2 ; $-C_{1-4}$ alkyl; $-C_{1-4}$ alkylene- R^7 ; $-C_{2-4}$ alkenylene- R^7 ; $-C_{2-4}$ alkynylene- R^7 ; R^7 ; OR^7 (where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^7 is optionally substituted by R^a and/or R^b); C_{2-4} alkenyl; halogen; $-(CH_2)_yCOOR^8$ (where $y = 0-3$ and R^8 represents

H, C₁₋₄alkyl, or C₂₋₄alkenyl); -CONR⁹R¹⁰ (where R⁹ and R¹⁰ independently represent H, C₁₋₄alkyl, C₂₋₄alkenyl, -O-C₁₋₄alkyl, -O-C₂₋₄alkenyl or

-C₁₋₃alkylenePh (wherein Ph is optionally substituted by R^a and R^b as hereinabove defined); -CON(R¹¹)OR¹² (where R¹¹ and R¹² independently represent H, C₁₋₄alkyl or C₂₋₄alkenyl);

a group of the Formula II: -CONR¹³-CR^{13a}R¹⁴-COOR¹⁷, (where R¹³ and R^{13a} are independently H or C₁₋₄alkyl, R¹⁷ is H or C₁₋₆alkyl, R¹⁴ is selected from the side chain of a lipophilic amino acid, carbamoylC₁₋₄alkyl, N-(monoC₁₋₄alkyl)carbamoylC₁₋₄alkyl and N-(diC₁₋₄alkyl)carbamoylC₁₋₄alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula:

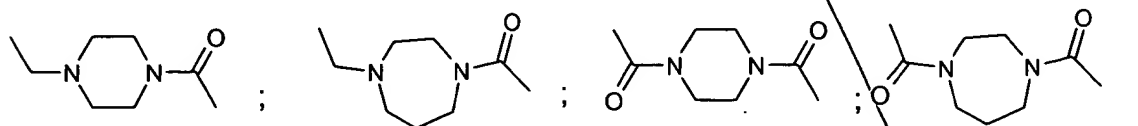


C₁₋₄alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R¹⁵ (where X is selected from O, CO, CH₂, S, SO, SO₂ and R¹⁵ is selected from C₁₋₆alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R¹⁵ is optionally substituted by R^a and/or R^b;

p is 0-3 in which R³ values can be the same or different;

G is a linking moiety selected from the following groups written from left to right in Formula I:



Sub 01

(wherein the piperazine and perhydro-1,4-diazepine rings are optionally substituted);
-CO-NR¹⁶-; -CH₂-NR¹⁶-; -CH₂S-; -CH₂O-; -CH₂-CHR¹⁶; -CH=CR¹⁶-; -CH₂NR¹⁶-T-;
-CH₂NR¹⁶-SO₂-; -CH₂-NR¹⁶-CO-T¹-; -CO-NR¹⁶-T-; -CH₂S-T-; -CH₂O-T- (where R¹⁶ is
selected from H, C₁₋₄alkyl, C₁₋₄alkylene-Z, -CO-C₁₋₄alkylene-Z, -CO-C₁₋₆alkyl, -COZ, Z
and Z is selected from -O-C₁₋₄alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or
bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and
any aryl ring in R¹⁶ is optionally substituted by R^a and/or R^b as hereinabove defined;
where, T represents -(CH₂)^m- where m is 1-4 and T is optionally monosubstituted with
any value of R¹⁶ other than H; and
where T¹ represents -(CH₂)^{m¹}- wherein m¹ is 0-4 and T¹ is optionally monosubstituted
with any value of R¹⁶ other than H);
A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl
ring containing up to 5 heteroatoms where the heteroatoms are independently selected
from O, N & S;
or a -S-S- dimer thereof when R²=H; or a N-oxide thereof; or a pharmaceutically
acceptable salt, prodrug or solvate thereof.

Please amend the first paragraph on page 4, line 10 to page 6, line 11, as
follows:

Sub 02

In another aspect of the invention there is provided an inhibitor of ras
farnesylation of Formula I
wherein:

~~8~~

Sub
D²

R^1 is selected from H; $-C_{1-4}$ alkyl; $-C_{1-3}$ alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from C_{1-4} alkyl, halogen, OH, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, thiol, C_{1-4} alkylsulfanyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl and sulfonamido; $-\text{CO}-C_{1-4}$ alkyl; $-\text{CO}-\text{O}-C_{1-4}$ alkyl; $-\text{CO}-\text{O}-C_{2-4}$ alkenyl; $-\text{CO}-\text{O}-(\text{CH}_2)_n\text{Ph}$ optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}$ alkylene-Ph above and $n=0-4$; $-C_{1-4}$ alkylene- CONR^4R^5 where R^4 & R^5 are independently selected from H and C_{1-4} alkyl; and $-C_{1-4}$ alkylene- COOR^6 where R^6 is selected from H, C_{1-4} alkyl;

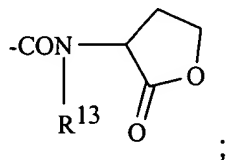
R^2 is selected from H; $-C_{1-4}$ alkyl; $-C_{1-3}$ alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}$ alkylene-Ph above; $-\text{COC}_{1-4}$ alkyl; and $-\text{COOC}_{1-4}$ alkyl;

R^3 is selected from H; OH; CN; CF_3 ; NO_2 ; $-C_{1-4}$ alkyl; $-C_{1-4}$ alkylene- R^7 where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^7 is optionally substituted as defined for substitution on the Ph group in $R^1 = -C_{1-3}$ alkylene-Ph above; R^7 ; C_{2-4} alkenyl; halogen; $-(\text{CH}_2)_y\text{COOR}^8$ where $y = 0-3$ and R^8 represents H, C_{1-4} alkyl, or C_{2-4} alkenyl; $-\text{CONR}^9\text{R}^{10}$ where R^9 and R^{10} independently represent H, C_{1-4} alkyl, C_{2-4} alkenyl, $-\text{O}-C_{1-4}$ alkyl, $-\text{O}-C_{2-4}$ alkenyl, $-C_{1-3}$ alkylenePh optionally substituted as defined for this group for R^1 above; $-\text{CON}(\text{R}^{11})\text{OR}^{12}$ where R^{11} and R^{12} independently represent H, C_{1-4} alkyl and C_{2-4} alkenyl;

a group of Formula II, $-\text{CONR}^{13}-\text{CHR}^{14}-\text{COOR}^{17}$, where R^{13} is H or C_{1-4} alkyl, R^{17} is H or C_{1-6} alkyl, R^{14} is selected from the side chain of a lipophilic amino acid,

carbamoylC₁₋₄alkyl, N-(monoC₁₋₄alkyl)carbamoylC₁₋₄alkyl and N-(diC₁₋

4alkyl)carbamoylC₁₋₄alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



C₁₋₄alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R¹⁵ where X is selected from O, CO, CH₂, S, SO, SO₂ and R¹⁵ is selected from C₁₋₆alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R¹⁵ is optionally substituted as defined for the Ph group in R¹ = -C₁₋₃alkylene-Ph; p is 0-3 in which R³ values can be the same or different;

G is a linking moiety selected from the following groups written from left to right in

Formula I:

-CO-NR¹⁶- where R¹⁶ is selected from H, C₁₋₄alkyl, C₁₋₄alkylene-Z, -CO-C₁₋₄alkylene-Z,

-CO-C₁₋₆alkyl, -COZ, Z and Z is selected from -O-C₁₋₄alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms

selected from O, N and S and any aryl ring in R¹⁶ is optionally substituted as defined for

the Ph group in R¹ = -C₁₋₃alkylene-Ph; -CH₂-NR¹⁸- where R¹⁸ represents any value

defined for R¹⁶; -CH₂S-; -CH₂O-; -CH₂-CHR¹⁹- where R¹⁹ represents any value defined

for R¹⁶; -CH=CR²⁰- where R²⁰ represents any value defined for R¹⁶; -CH₂NR²¹-T- where

R²¹ represents any value defined for R¹⁶, T represents -(CH₂)_w- where w is 1-4 and T is

optionally monosubstituted with R²² where R²² represents any value for R¹⁶ other than

H; -CH₂NR²³-SO₂- where R²³ represents any value defined for R¹⁶; -CH₂-NR²⁴-CO-T-

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000

~~where R^{24} represents any value defined for R^{16} , T represents $-(CH_2)_w$ where n is 0-4 and T is optionally monosubstituted with R^{29} where R^{29} represents any value for R^{16} other than H; $-CO-NR^{25}-T-$ where R^{25} represents any value defined for R^{16} , T represents $-(CH_2)_w$ where w is 1-4 and T is optionally monosubstituted with R^{26} where R^{26} represents any value for R^{16} other than H; $-CH_2S-T-$ where T represents $-(CH_2)_w$ where w is 1-4 and T is optionally monosubstituted with R^{27} where R^{27} represents any value for R^{16} other than H; $-CH_2O-T-$ where T represents $-(CH_2)_w$ where w is 1-4 and T is optionally monosubstituted with R^{28} where R^{28} represents any value for R^{16} other than H;~~

~~A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N & S;~~

~~or a $-S-S-$ dimer thereof when $R^2=H$; or a N-oxide thereof;~~

~~or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof.~~

Please amend the second paragraph on page 9, line 7 to page 9, line 20, as follows:

Preferably R^1 is selected from H; $-CO-O-(CH_2)_nPh$ optionally substituted on phenyl hereinabove defined; $-CO-O-C_{2-4}alkenyl$; $-CO-C_{1-4}alkyl$; $-C_{1-4}alkylene-CONR^4R^5$ where R^4 and R^5 are independently selected from H, $C_{1-4}alkyl$.

Most preferably R^1 is hydrogen.

Preferably R^2 is selected from H and $-CO-C_{1-4}alkyl$.

3
Most preferably R^2 is hydrogen.

Preferably G is selected from $-CH_2-NR^{16}-$ and $-CH_2NR^{16}-T$.

Preferably A is selected from phenyl, naphthyl, pyridyl and thienyl.

Most preferably A is phenyl or naphthyl.

Preferably combinations of R^3 and p are selected from:

- i) R^3 is selected from a group of Formula II, $-C_{1-4}alkylR^7$, $-O-R^7$ and R^7 ; and $p=1-3$ with the proviso that at least one of R^3 is a group of the Formula II;
- ii) $p=0$ with the proviso that A is naphthyl and G is $-CH_2NR^{16}-T$; and
- iii) $p=1$ with the proviso that R^3 = a group of Formula II and A is phenyl or naphthyl.

Please amend the first paragraph on page 10 line 4 to page 10, line 15, as follows:

4
Sub
D3
Suitable values for $G=CHNR^{16}T$ include $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH_2$;
 $CH_2.N(CH_2.CH_2.CH_2.OMe).CH_2.CH_2$; $CH_2.N(CH_2.pPh.OMe).CH_2.CH_2$;
 $CH_2.N(CO.CH_2.CHMe_2).CH_2$; $CH_2N(CO.CH_2.CH_2.CH_2.Me).CH_2$;
 $CH_2N(CO.CH_2.CHMe.CH_2Me).CH_2$; $CH_2N(CO.CH_2.CH_2.OMe)CH_2$;
 $CH_2N(CO.CH_2.pyridin-3-yl).CH_2$; $CH_2N(4-methoxybenzyl)CH_2$;
 $CH_2N(CO.CH_2.CHMe_2)CH_2.CH_2.CH(Ph)$; $CH_2N(CO.CH_3)CH_2.CH_2.CH(Ph)$;
 $CH_2N(CO.CH_2.CHMe_2)CH_2$; $CH_2N(CO.CH_3)CH_2$; $CH_2N(CO.CH_2.CHMe_2)CH_2.CH(Ph)$;
 $CH_2N(CO.CH_2.CMe_3)CH_2.CH(Ph)$; $CH_2N(CO.CH_2.pyridin-3-yl)CH_2.CH(Ph)$;
 $CH_2N(CO.1-hydroxy-6-methoxy-pyridin-3-yl)CH_2.CH(Ph)$; $CH_2N(CO.CH_2.pyrid-3-yl)CH_2CH(Ph)$; $CH_2N(CO.CH_2CHMe_2)CH_2.CH_2$; $CH_2N(CO.CH_2CMe_3)CH_2.CH_2$;

Sub
03

$\text{CH}_2\text{N}(\text{CO thiazol-2-yl})\text{CH}_2\text{CH}_2$; $\text{CH}_2\text{N}(\text{CO 1-oxido-6-hydroxypyridin-3-yl})\text{CH}_2\text{CH}_2$;
 $\text{CH}_2\text{N}(\text{CO.CH}_2\text{pyridin-3-yl})\text{CH}_2.\text{CH}_2$ and $\text{CH}_2\text{N}(\text{CO.4-methoxybenzyl})\text{CH}_2.\text{CH}_2$.

Please amend the third paragraph on page 10, line 20 to page 10, line 22, as follows:

Sub
04

Suitable values for $\text{G} = -\text{CH}_2\text{NR}^{16}-$ include CH_2NH ; CH_2NMe ;
 $\text{CH}_2\text{N}(\text{CO.CH}_2.\text{CHMe}_2)$ and $\text{CH}_2\text{N}(\text{CO.CH}_2.\text{CH}_2.\text{OMe})$. A preferred value for $-\text{CH}_2\text{NR}^{16}-$ is $-\text{CH}_2\text{NH}_2-$.

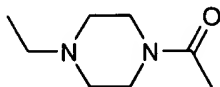
Please amend the fourth paragraph on page 10, line 23 to page 10, line 26, as follows:

Sub
05

When G is $-\text{CH}_2\text{NR}^{16}-\text{T}-$ a suitable value for m is 1. When G is $-\text{CH}_2-\text{NR}^{16}-\text{CO}-\text{T}^1-$ a suitable value for m^1 is 1. When G is $-\text{CH}_2-\text{NR}^{16}-\text{T}-$ a suitable value for m is 1. When G is $-\text{CH}_2-\text{S}-\text{T}-$ a suitable value for m is 1. When G is $-\text{CH}_2-\text{O}-\text{T}-$ a suitable value for m is 1. G is especially $-\text{CONH}-$, $-\text{CH}_2-\text{NH}-$, $-\text{CH}_2\text{NHSO}_2-$, $-\text{CH}_2\text{NHCO}-$.

Please amend the fifth paragraph on page 10, line 27 to page 11, line 5, as follows:

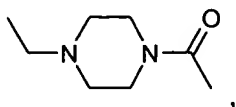
In another aspect G is of the formula



wherein the piperazine ring is optionally substituted by $\text{C}_{1-4}\text{alkoxyC}_{1-4}\text{alkyl}$,
 $\text{phenoxyC}_{1-4}\text{alkyl}$ or $\text{heteroaryloxyC}_{1-4}\text{alkyl}$.

Please amend the first paragraph on page 11, line 1 to page 11, line 5, as follows:

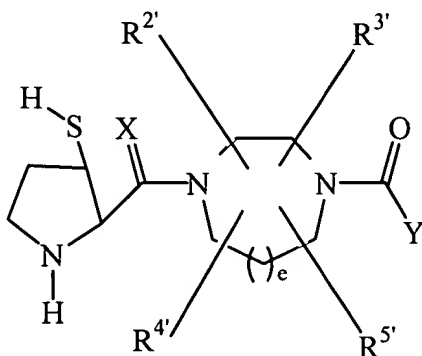
8
Preferably, when G is of the formula



A is naphthyl.

Please amend the first paragraph on page 19, line 20 to page 21, line 21, as follows:

9
In another aspect of the present invention there is provided a compound which inhibits farnesyl-protein transferase of the formula B:



wherein:

X is O or H₂;

e is 0 or 1;

t is 1 to 4;

R^{2'}, R^{3'}, R^{4'}, and R^{5'} are independently selected from: H; C₁₋₈alkyl, alkenyl, alkynyl, aryl, heterocycle, -CO-NR^{6'}R^{7'} or -CO-OR^{6'}, unsubstituted or substituted with one or more of:

79
1) aryl or heterocycle, unsubstituted or substituted with:

- a. C_{1-4} alkyl,
- b. $(CH_2)_tOR^{6'}$,
- c. $(CH_2)_tNR^{6'}R^{7'}$,
- d. halogen,

2) C_{3-6} cycloalkyl,

3) $OR^{6'}$,

4) $SR^{6'}$, $S(O)R^{6'}$, $SO_2R^{6'}$,

5) $-NR^{6'}R^{7'}$,

6) $-NR^{6'}-CO-R^{7'}$,

7) $-NR^{6'}-CO-NR^{7'}R^{8'}$,

8) $-O-CO-NR^{6'}R^{7'}$,

9) $-O-CO-OR^{6'}$,

10) $-O-NR^{6'}R^{7'}$,

11) $-SO_2NR^{6'}R^{7'}$,

12) $-NR^{6'}-SO_2-R^{7'}$,

13) $-CO-R^{6'}$, or

14) $-CO-OR^{6'}$;

and any two of $R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are optionally attached to the same carbon atom;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:

- a. C_{1-4} alkoxy,
- b. $NR^{6'}R^{7'}$,

- 789
- c. C₃₋₆cycloalkyl,
 - d. aryl or heterocycle,
 - e. HO,

- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR^{6'},
- 5) NR^{6'}R^{7'},
- 6) CN
- 7) NO₂, or
- 8) CF₃;

R^{6'}, R^{7'} and R^{8'} are independently selected from: H; C₁₋₄alkyl, C₃₋₆cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- a) C₁₋₄alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,
- e) -CO-R^{9'},
- f) -SO₂R^{9'}, or
- g) NRR¹, wherein

R^{6'} and R^{7'} may be joined in a ring, and

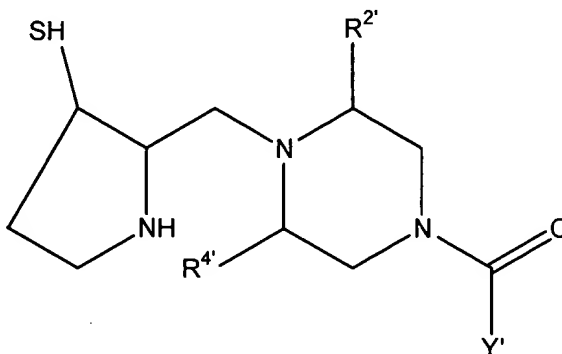
R^{7'} and R^{8'} may be joined in a ring;

R^{9'} is C₁₋₄alkyl or aralkyl;

or a optical isomer, disulfide or pharmaceutically acceptable salt thereof.

Please amend the first paragraph on page 21, line 22 to page 22, line 2, as follows:

¹⁰
B A preferred subclass of the formula B is:



wherein R^{2'} and R^{4'} are independently hydrogen and Y' is C₁₋₄alkyl, phenyl or a 5 or 6 membered heteroaryl ring containing up to 3 heteroatoms selected from N, O and S or of the formula -C₁₋₄alkyl OR^{10'} wherein R^{10'} is C₁₋₄alkyl, phenyl or 5 or 6-membered heteroaryl containing up to 3 heteroatoms selected from N, O and S. Preferably R^{10'} is C₁₋₄alkyl.

¹¹
C Please amend the first paragraph on page 22, line 3, as follows:

Preferably Y' is naphthyl.

I Please amend the second paragraph on page 22, line 4 to page 22, line 18, as follows:

¹²
D The aspect of the invention relating to Formula B involves compounds related to those disclosed PCT patent application WO 95/00497 (Graham et al.); see the complete specification and claim 1 in particular. Formula B above is based on Formula A in WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidine moiety of the

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

present invention replacing the cysteine-like moiety on the left hand side of Formula A in WO 95/00497 (Graham et al.). Optionally the nitrogen and/or thiol atoms in the pyrrolidine moiety of Formula B may be substituted by taking the values for R^1 and R^2 in Formula I as set out herein. Compounds within the scope of Formula B may be prepared by a skilled person using the synthetic details in WO 95/00497 (Graham et al.) combined with the present specification. Preferred compounds for this aspect of the invention correspond to those set out in claims 6-12 of WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidin-2-yl-methyl moiety of the present invention replacing the HS-CH₂-CH(NH₂)-CH- moiety on the left hand side of the relevant compounds attached to the piperazine ring as drawn out in the claims. A preferred compound is (2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine; see Example 7 herein.

Please amend the first paragraph on page 32, line 4 to page 32, line 24, as follows:

Compounds of Formula I in which G represents -CO-NR¹⁶- may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 1.

Compounds of Formula I in which G represents -CO-NR¹⁶-T- may be prepared by an analogous procedure. Suitable coupling conditions include the following:

i) Use of EEDQ at ambient temperature in an organic solvent (e.g. dichloromethane, methanol).

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

213
Sub
06

ii) Use of oxalyl chloride in an organic solvent (e.g. CH_2Cl_2), DMF in a catalytic amount, in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at 0°C to ambient temperature for 0.5-16h.

iii) Use of EDC/HOBT in an organic solvent (e.g. DMF, CH_2Cl_2).

iv) Use of DCC/HOBT in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. triethylamine).

v) Use of mixed anhydride reactions under standard conditions, for example isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).

vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).

vii) Via an acid chloride under standard conditions e.g. using thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

Please amend the second paragraph on page 32, line 24 to page 33, line 3, as follows:

214
Sub
07

Compounds of Formula I in which G represents $-\text{CH}_2\text{NR}^{16}-$, $-\text{CH}_2\text{O}-$ or $-\text{CH}_2\text{S}-$ may be prepared as outlined in Scheme 2. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or NR^{16} . Suitable coupling conditions include the following.

- 14
Sub
.07
- i) Use of an inorganic base (e.g. NaHCO_3 , NaH , K_2CO_3 , butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a temperature of about 65° to 150°C
- ii) Use of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature - 150°C
- iii) Use of an inorganic base (e.g. KOH , NaOH , K_2CO_3) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

Please amend the first paragraph on page 33, line 4 to page 33, line 12, as follows:

15

Compounds of Formula I in which G represents $-\text{CH}=\text{CR}^{16}-$ may be prepared using a Wittig reaction as outlined in Scheme 3. Suitable reaction conditions include the following.

- i) Use of a base (e.g. potassium carbonate, metal hydride, metal alkoxide) in the presence of an organic solvent (e.g. THF, toluene, DMSO) optionally in the presence of an aqueous solvent (2-phase system) and optionally in the presence of a catalyst complexing agent which solubilises alkali metal ions in non-polar solvents such as 1,4,7,10,13-pentaoxacyclopentadecane (also called 15-Crown-5) or 1,4,7,10,13,16-hexaoxacyclooctadecane (also called 18-Crown-6).

Please amend the second paragraph on page 33, line 13 to page 33, line 18, as follows:

B16
Sub
08

Compounds of Formula I in which G represents $\text{-CH}_2\text{-NR}^{16}$ - may be prepared as outlined in Scheme 4 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.

i) Use of reducing agent (e.g. NaCNBH_3 , BH_3 , hydrogen plus catalyst, LiHBEt_3 , di-isobutyl-aluminiumhydride, lithium aluminium hydride, sodium borhydride) in the presence of suitable solvent e.g. ethanol and acetic acid.

Please amend the fifth paragraph on page 33, line 28 to page 34, line 2, as follows:

B17
Sub
09

Compounds of Formula I in which G represents $\text{-CH}_2\text{-NR}^{16}\text{-T-}$, $\text{-CH}_2\text{-O-T-}$ or $\text{-CH}_2\text{-S-T-}$ may be prepared as outlined in Scheme 5 in which LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents O, S or NR^{16} . Suitable coupling conditions are as outlined above in relation to Scheme 2. Optionally the positions of LG and XH in compounds 1 and 2 in Scheme 5 can be reversed to give the same end product.

Please amend the first paragraph on page 34, line 3 to page 34, line 10, as follows:

B18

Compounds of Formula I in which G represents $\text{-CH}_2\text{-NR}^{16}\text{-SO}_2\text{-}$ may be prepared as outlined in Scheme 6. Compounds 1 and 2 may be coupled under standard conditions such as the following.

Q18 i) Use of an organic base (e.g. di-isopropyl-ethylamine, triethylamine, 4-methyl-morpholine) in the presence of an organic solvent (e.g. dichloromethane) at a temperature range of 0°- 40° C.

ii) Use of an inorganic base (e.g. potassium carbonate) in the presence of an organic solvent (e.g. DMF) at a temperature range of 0° - 150° C

Please amend the second paragraph on page 34, line 11 to page 34, line 13, as follows:

Q19 Compounds of Formula I in which G represents $-\text{CH}_2\text{-NR}^{16}\text{-CO-T-}$ may be prepared as outlined in Scheme 7. Compounds 1 and 2 may be coupled under standard conditions such as described above for $\text{G} = -\text{CO-NR}^{16}-$.

Please amend the third paragraph on page 34, line 14 to page 34, line 18, as follows:

Q20 Compounds of Formula I in which G represents $-\text{CH}_2\text{-CHR}^{16}-$ may be prepared by reduction of compounds of the type set out as compound 3 in Scheme 3. Reduction is carried out under standard conditions with standard reagents for example using hydrogenation in the presence of a catalyst such as palladium on charcoal at ambient temperature.

Please amend the fourth paragraph on page 34, line 19 to page 34, line 23, as follows: